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TITLE: Racial Differences in Prostate Cancer: Influences of Health Care Interaction and Host and Tumor Biology

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13. ABSTRACT *(Maximum 200 Words)* The purpose of the Development Award Proposal was to form a Consortium of nine institutions to conduct a comprehensive study of men with newly diagnosed prostate cancer (CaP) that exhibit different CaP mortality rates-500 North Carolina African Americans (high risk), 500 Louisiana African Americans (intermediate risk) and 1000 Caucasian Americans in both states (low risk). The *scope* of the proposed studies is to categorize the relative contributions to CaP mortality from racial differences in: 1) interaction with the health care system; 2) biology of the host; and 3) characteristics of the tumor. The Development Award allowed us to submit a Consortium proposal that was approved for funding; assemble a team of investigators, administrative structure and scientific and lay oversight committees to facilitate the proposed studies; pilot our methods in a small study that demonstrated that men of both races in both states would participate in the proposed studies; verify that research specimens were suitable for the analyses proposed; improve the method for measurement of apoptosis in CaP; demonstrate diagnostic prostate biopsies could be microarrayed; assemble the interview instruments; formulate a plan to meet the new HIPA requirements; and begin the development of the central Consortium database.

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RACIAL DIFFERENCES IN PROSTATE CANCER: INFLUENCE OF HEALTH CARE INTERACTION AND HOST AND TUMOR BIOLOGY

INTRODUCTION

The *subject* of the Development Award Proposal was the disproportionate mortality from prostate cancer (CaP) in African Americans (AA) compared to Caucasian Americans (CA). The *purpose* of the Development Award Proposal was to form a Consortium to conduct a comprehensive study of a large number of men with newly diagnosed CaP from two geographic areas where prostate cancer mortality not only differs between races but also between the two AA groups. The *scope* of the proposed studies will address directly racial differences in CaP since AA in North Carolina (NC) have one of the highest, and AA in Louisiana (LA) have one of the lowest mortality rates from CaP in the United States while CA in the two states have similar CaP mortality that is less than either AA group. The Consortium will test the hypothesis that the mortality rate from CaP is more than two-fold higher in AA compared to CA due to racial differences in: 1) interaction with the health care system evaluated by examining early detection behavior; socioeconomic status; attitudes, beliefs and knowledge; health care access; patient-physician communication; patient decision-making; alternative treatment use and treatment choices; 2) diet with an emphasis upon antioxidant and fat consumption and biology of the host with an emphasis upon serum androgens; exposure to carcinogens; expression of CaP susceptibility genes such as androgen metabolism pathway, detoxification, DNA repair and hereditary CaP genes; and serum protein profiles associated with the aggressive CaP phenotype; and/or 3) characteristics of the tumor such as tumor extent (clinical stage and serum prostate-specific antigen (PSA), a tumor volume surrogate), tumor differentiation (Gleason grade) and tumor growth rate (apoptosis and cellular proliferation); expression of androgen receptor, androgen receptor co-activators and androgen-regulated genes; and stem-like cells. Investigators from the University of North Carolina (UNC), Louisiana State University Health Sciences Center (LSUHSC), Wake Forest University, Harvard University, Boston University, Johns Hopkins Medical Center, University of South Carolina, National Institute for Environmental Health Sciences, National Cancer Institute and Food and Drug Administration have joined together to address critical aims in a large cohort of patients with newly-diagnosed CaP. Two thousand patients, 1000 from NC of whom 500 are AA and 500 are CA, and 1000 from LA of whom 500 are AA and 500 are CA, will be identified by rapid case ascertainment and undergo in-home interview and blood and adipose tissue sampling within 90 days of diagnosis. Tissue microarrays will be constructed from diagnostic biopsy specimens. The Development Award allowed us to 1) pilot the home visit and research specimen analyses; 2) develop further our tissue microarray methods; and 3) prepare the Consortium Award Proposal.

BODY

Task 1) Pilot the In-home Interview

a. Obtain all forms, instruments and questions necessary to obtain all data for all investigators

All investigators of the 12 proposals submitted for the Consortium were surveyed concerning the information required from the subjects. The first survey was very general to order to broadly identify these areas. The second survey was more specific with instruments presented to the investigators and selections determined. The focus was on instruments that would be used across a number of the studies. Nine measures were selected to pilot in addition to the instruments to be used in level 1 studies (Projects 1 and 2). The measures included topics that could serve as alternative hypotheses for some studies including measures of pesticide exposure, body size measurements and pubescent development. Other measures will provide background information for investigators and include information on demographic and income variables, other illness history, and family history. A third grouping of measures focus on the process of diagnosis including the screening history and medical tests and the process of reaching a care decision. The instruments selected for potential inclusion were submitted as part of the DOD Consortium Award proposal.

b. Modify the computer-assisted in-home interview instrument to obtain all data

Now that the instrument packet has been identified, it can soon be developed into the in-home interview and pilot tested for feasibility and practicality. We will place the instruments onto the portable computers that already contain the dietary instrument once a decision is reached upon the funding of Project 1. We will pilot the complete instrument using standing focus groups available to us through our partnership with North Carolina Central University (NCCU) prior to evaluation in focus groups of AA and CA men with CaP in NC and LA.

c. Pilot the instrument to determine the feasibility of obtaining all desired data

Although the interview instrument remains in evolution, we sought to determine the feasibility of our entire research data accrual strategy. UNC and LSUHSC conducted a pilot study from March-May, 2002 on incident cases of CaP of both races in both states to test feasibility of all aspects of recruitment, field work, nurse training, sample collection, handling and transport procedures, and research subject participation. The goal of the pilot study was to assess the success of subject recruitment methods and to determine the willingness of subjects to participate in all aspects of the study. Two videotapes were produced: a 25 minute training video for research nurses and a 3 minute video for consenting research subject. Gayle Grigson, clinical research nurse at UNC and Dr. Mohler, Consortium Director, trained 2 nurses at UNC and 1 nurse at LSUHSC to conduct the in-home visits. Due to the limited turnaround time between funding of the pre-proposal and the proposal due date, we were unable to conduct a complete registry-based subject sampling. The time window for scheduling home visits was less than 2 weeks for most individuals. Scheduling choices and research nurse resources were limited on such short notice. Despite this, over 50% participation rate was found in each race and state. In NC, the cases were population-based; in LA, a convenience sample of newly diagnosed cases from select urologists was used. Research nurses conducted home interviews on 38 research subjects during which they obtained written, informed consent, conducted the computer-based diet questionnaire, and obtained blood, adipose tissue, urine, and toenail samples. This pilot was useful in refining the field procedures and quality control. It also helped identify the questions and responses of the subjects to the study.

Participation results are demonstrated in Table 1. Three men refused the blood or adipose tissue sampling procedure due to wording in the consent form at UNC.

Table 1. Pilot Study: Research Subject Participation

State	Race	Agreed to Home Visit	All Data Collected	Age Range (yrs)
LA	AA	15/15	14/15*	37-85
	CA	4/4	4/4	52-79
NC	AA	8/9	7/9	56-78
	CA	10/11**	10/10	53-81

* One subject agreed to participate but developed pneumonia on the day of the scheduled visit.

** One research subject could not be reached based on the contact information provided by his physician.

d. Generate an in-home interview that meets the requirements for data generation within the bounds of practicality

See above.

Task 2) Microarray Diagnostic Prostate Biopsies and Immunostain for Molecules of Interest

a. Complete on-going projects to 1) measure the heterogeneity of Ki-67 and androgen receptor expression in radical prostatectomy specimens compared to diagnostic prostate biopsies from the same patient and 2) determine the number of sections that can be cut from a microarray block constructed from punch biopsies of prostate needle biopsies

1) measure the heterogeneity of Ki-67 and androgen receptor expression in radical prostatectomy specimens compared to diagnostic prostate biopsies from the same patient

We created 2 tissue microarrays from radical prostatectomy specimens from 23 men (12 AA and 11 CA). For example, tissue microarray 1 contains the specimens from 12 men who have from 2-39 0.6mm cores from CaP that resulted in acquisition of 6-107 digital images per patient. Each image provided approximately 30 malignant nuclei for analysis. During the past year, artifacts due to fixation have been identified that were avoided since all specimens were from the prostate periphery. The need for internal and external controls was fortunately met by the inclusion of rat liver on both tissue microarrays and benign prostate tissue in all specimens. Others have reported that Ki-67 can be measured accurately by obtaining 4 cores per patient.[1-5] Since androgen receptor immunostaining is more variable than Ki-67 expression, we chose to determine the sampling strategy necessary to capture the heterogeneity of androgen receptor expression. The objective of the current analysis is to estimate the contribution of the different sources of variation to the variability of androgen receptor expression measured by both mean optical density (MOD) and percent positive nuclei (PPN). Data from two tissue microarrays are being used. Each tissue microarray's data are analyzed separately. The data have a nesting structure; there are several cores within each block, and several blocks within each patient. The total variance is broken down into variability between subjects, variability between blocks within a subject, and variability between cores within a block. The analysis will be complete next week. The next step is to use the variance-components estimates to compare the precision that can be obtained with different choices of numbers of blocks and cores per block, so that an optimal combination of these can be used to create tissue microarrays from radical prostatectomy specimens from a large number of men. Pertinent to the proposed studies is comparison of Ki-67 and androgen receptor immunostaining between radical prostatectomy specimens and the diagnostic prostate biopsies from the same man. We will create a tissue microarray from the diagnostic prostate biopsies using a strategy inferred from the analysis of radical prostatectomy specimens. The sources of variance in prostate biopsies will be analyzed and their similarity or differences compared to the radical prostatectomy specimen will be determined.

2) determine the number of sections that can be cut from a microarray block constructed from punch biopsies of prostate needle biopsies

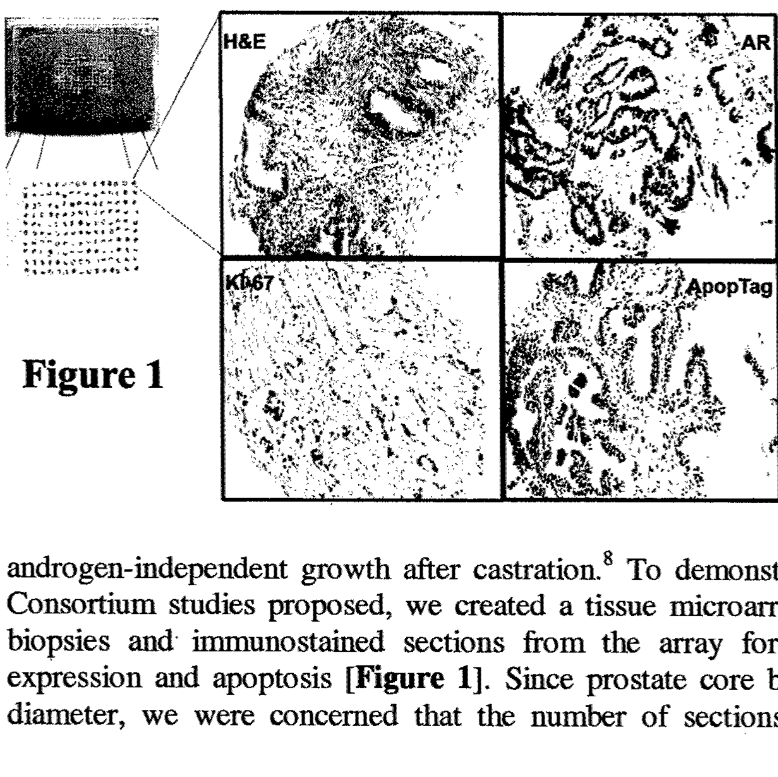


Figure 1

We have microarrayed in one block each 25 specimens of recurrent CaP, 110 CWR22 xenografts and 640 radical prostatectomy specimens. We have used these tissues to assess AR[6] and IGFBP[7] protein levels, apoptosis, cell proliferation[6] and genes expressed coincidentally with the onset of androgen-independent growth after castration.[8] To demonstrate feasibility of the DOD Consortium studies proposed, we created a tissue microarray from diagnostic prostate biopsies and immunostained sections from the array for AR protein levels, Ki-67 expression and apoptosis [**Figure 1**]. Since prostate core biopsies are only 1.3 mm in diameter, we were concerned that the number of sections that could be cut from a microarray of prostate biopsies would be less than from larger specimens such as radical prostatectomies. However, in our first effort, we serially sectioned at 0.6 μm thickness a tissue microarray block constructed from 150 cores of benign prostate biopsies. H&E sections contained >80% of cores through 36 sections **[Figure 2]**.

b. Develop automatic sampling of tissue microarrays by automation of our motor-driven stage, image analysis for recognition of tissue samples and registration of x, y-coordinates of each tissue sample

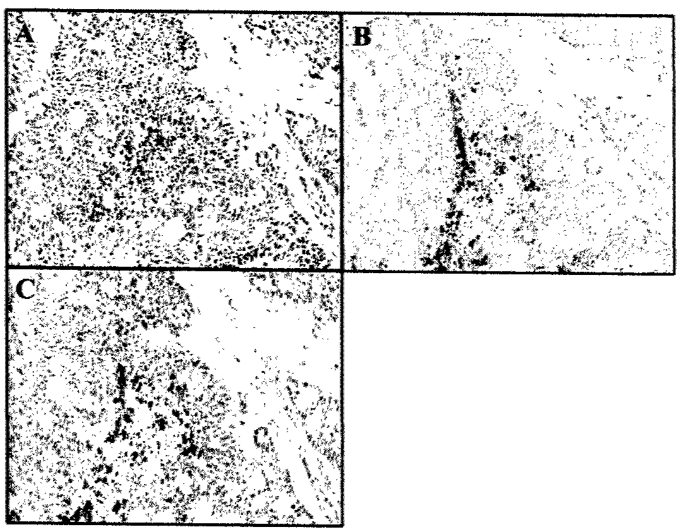
The imaging system consists of Leica DMRA2 microscope with Ludl MAC5000 stage controller and Hammatsu C5810 color chilled 3CCD camera. The images can be viewed on 13" Sony Trinitron monitor. The stage controller is automated and can be controlled by the computer. However, automated selection of cores in a microarray is not possible with this setup. Images are acquired using Image Pro 4.5 on a Pentium IV based PC running Windows 2000. Images are viewed and stored with a 24-bit color resolution of 640x480 pixels. Analysis of the images is also done on three other Pentium IV based PCs running Windows 2000. Macros written in Image Pro compute color parameters, which were previously obtained using Optimas. Computation of MOD is done on Xeon based workstation running Linux 7.0. Work is ongoing to convert the programming in Linux to a Windows platform so programs on Windows platform can perform the entire analysis.

If we cannot use Image Pro for this application, we may consider purchase of a system by ChromoVision that should come to market soon that will combine automated acquisition of tissue microarray images and image analysis. In addition, we have initiated a collaboration with Angelo M. DeMarzo, MD, Ph.D., Johns Hopkins Medical Institutions, whose group can scan our immunostained tissue microarray sections, store the images as JPEGs (although whether this can be done as TIFs remains uncertain) using a BLISS Workstation and transmit them to us over the internet for image analysis. A relational database (open source, JAVA) is under development by Dr. DeMarzo's group that will allow image storage, image analysis, data storage and data analysis.

We have identified a potential problem with the appropriateness of using TUNEL for measurement of apoptosis that is important for accurate determination of tumor growth rate, one of the common endpoints for the proposed studies. The extent of apoptosis in prostate tissue even after androgen ablation has been hotly debated.[9-13] TUNEL does not differentiate between apoptotic and necrotic cells since both processes fragment DNA.[14] In addition, erroneous TUNEL results can result from activity of endogenous endonucleases released during proteinase K incubation[15] and H_2O_2, detergent and heat treatments that are part of the TUNEL protocol[16,17] and unavailable 3′-OH ends for labeling due to DNA compaction or crosslinking.[18] Caspase-3 has been reported to participate in numerous cell death cascades[19] and is necessary for DNA fragmentation during apoptosis.[20] Decreased expression of caspase-3 was found in androgen-dependent CaP compared to BPH.[21] Marshman and associates[22] reported higher correlation between apoptosis and caspase-3 expression than TUNEL when apoptosis was recognized by the presence of apoptotic bodies.

We developed a method for measurement of apoptosis that relies upon detection of caspase-3 instead of TUNEL [**Figure 3**]. An anti-human caspase-3 antibody (rabbit polyclonal AF835, R&D Systems) recognizes the p17 active subunit and cross-reacts poorly with the precursor. We have optimized caspase-3 immunostaining using our prostate biopsy tissue microarray. Paraffin-embedded specimens are deparaffinized and rehydrated using Hemo-De and graded alcohols. Caspase-3 antigen is retrieved using citrate buffer. Endogenous peroxidases are blocked using H_2O_2 and other antigens are blocked using 5% normal goat serum and an avidin-biotin blocking kit (R&D Systems). Casapse-3 is recognized using polyclonal antibody (0.3 μg/mL; AF835; R&D Systems) for 1 hour at 37°C, biotinylated secondary antibody (anti-rabbit; 1:200; BA1000; Vector Labs) and avidin-biotin complex (1:200; PK6100; Vector Labs). The complex is visualized using DAB and counterstaining is performed using hematoxylin. Caspase-3 levels are quantified using immunohistochemical detection and video image analysis. We compared results with our proven method using ApopTag and the newer method using caspase-3 using the androgen-dependent CWR22 human CaP xenograft. Expression of caspase-3 reached a maximum on day 2 after castration, decreased on day 6 and remained low until tumor recurrence. The percentage of tumor area expressing caspase-3 increased from 2.51% ± 0.44% in tumors from intact mice to 20.84% ± 1.75% on day 2 after castration. Among immunopositive cells, the intensity of caspase-3 expression measured using the mean optical density (MOD) increased 45% (0.3762 ± 0.003 to 0.5461 ± 0.001) on day 2 after castration compared to levels detected in tumors from intact mice. Western blot analysis confirmed the results of immunodetection. TUNEL and caspase-3 immunodetection were compared directly using serial sections of a CWR22 tumor on day 2 after castration (magnification 200X) [**Figure 3**]. Merged images were generated that exhibited both TUNEL-positive and caspase-3-positive areas. The area of TUNEL staining (yellow: 5.65%) **(A)** exceeded that of caspase-3 (red: 3.32%) **(B)** that indicated caspase-3 is a more specific marker for apoptotic cells. An enhanced overlay composite **(C)** illustrated the co-localization (orange) of TUNEL (yellow) and caspase-3 (red). Although necrosis is rare in newly diagnosed CaP, apoptosis may be better measured using caspase-3 due to artifacts generated by the ApopTag method that lead to over-estimation of apoptosis.

Figure 3



Task 3) Develop a Prostate Cancer Consortium Award

a. Assemble the key personnel in Chapel Hill within one month of receiving the development award to discuss, evaluate and decide upon the construct and content of the consortium award proposal.

A DOD Consortium meeting was held at UNC February 22, 2002 (the agenda is Attachment 1). At this meeting, we discussed and/or acted upon the following:

- goal of the overall proposal and the role of each project within it
- proposal structure (thematic grouping, interaction matrix) and preparation guidelines
- hypothesis for each Project and function of each Core
- timeline
- samples and amount needed
- budget reduction from $15 to $10 million/ 3 years
- authorship and data sharing
- pilot project to demonstrate feasibility and uncover glitches

b. Develop the proposal with particular attention to creating central procedures for the handling of data (led by Dr. Schell, Director of the UNC-Lineberger Comprehensive Cancer Center Biostatistics Core), storage and analysis of blood, toenail, adipose tissue and diagnostic biopsies (led by Drs. Mohler and Smith, Co-directors of the UNC-Lineberger Comprehensive Cancer Center ImmunoAnalysis Core), and protection of patient confidentiality.

The central Consortium Database will provide a data management system accessible to all Consortium investigators at all sites. The system will support real-time data acquisition and transfer over robust, secure network connections. The system will also support batch data acquisition where network connectivity is inadequate. Three primary sources of data will be collected in this study: interviews, office-based medical records and direct measurements from tissue analyses. The information obtained regarding dietary and health habits, care access, and occupational and lifestyle exposures will be elicited by means of a computer-assisted interview, entered directly into that computer and stored on compact discs. In the event that a computer-assisted interview is not feasible due to logistics or system failure, information will be recorded on hard copy versions of the interview questionnaire. At the Consortium Database of Epidemiology Core 1, data will be downloaded onto the center's password-protected central computer. The compact discs will be stored under lock and key at a separate location in case it subsequently proves necessary to re-access the original data. Clinical data will be entered onto a standardized abstraction form that identifies each case only by their assigned study ID number and keypunched into the Consortium Database. Tissue data from the Scientific Cores and Projects will be transferred to the Consortium Database electronically.

Data from collection sites and laboratories will be consolidated and stored in a central Oracle database that will run on a mirrored server system with automatic fail-over features, daily backups, and transaction logs. Oracle Advanced Security features will be used for data transmission encryption and data integrity. Connections to the Oracle server will also be restricted by IP address where appropriate. Oracle audit logs will be reviewed routinely to verify the security measures are operational. The data tables will have access permissions defined at the user level, and multiple users will be able to access the central database simultaneously. In addition, Oracle views will be used to control access rights down to the field level.

A variety of ODBC-compliant clients will be used for the interfaces to the data, providing the most appropriate for the situation. All ODBC clients will be required to use encrypted transmission procedures on all data. A remote site with data-entry and report generation needs will use a client like Microsoft Access for flexible data querying and customized reports. Other sites that have occasional needs to view specific data may be better suited to a Web interface, and a statistical programmer may use SAS as a client to read subset data from the Oracle server. The SAS Internet® module will be used via a secure web connection (SSL) to provide collaborating researchers an easy, web-based interface for getting quick looks at appropriate data. Researchers will be able to do some preliminary analyses without requiring the assistance of a programmer. Data constraints, integrity checks, and triggered data changes will be implemented entirely in Oracle to preserve consistency across the various interfaces. All login connections to the Oracle database server(s) and the web server(s) will be restricted to secure, encrypted connections. Standard telnet and ftp services will be disabled and replaced with secure shell services and tunneling through secure connections. All other non-essential services will be disabled. The servers are currently maintained at the highest level of vendor and CERT security recommendations.

Blood and Tissue Procurement Core 2 performed a pilot study to determine the logistics of sample delivery, the yields of DNA and adipose tissue and the success rate of lymphocyte immortalization from the blood samples collected during home interviews by research nurses in NC and LA. The necessity for drive by delivery at both sites was recognized and incorporated into the protocol. Core 2 established that sufficient levels of DNA can be isolated from peripheral blood delivered to Core 2; DNA samples averaged 500 ug. Lymphocyte immortalization was successful on all samples from both sites. This demonstrates that lymphocytes can be obtained in LA, shipped overnight to NC and used for immortalization in NC. Adipose tissue samples averaged 15 mg per sample (range 4-35 mg) and were assayed successfully for myristic, myristoleic, palmitic, palmitelaidic, palmitoleic, stearate, oleic, linoleic, linolenic, eicosanoic, 11-eicosenoic, 11-14 eicosadienooic, homogamma linolenic, arachidonic, eicosapentaenoic (EPA), behenic, brassidic, 13-16 docosadienoic, 7-10-13-16 docosatetraenoic, 4-7-10-13-16 docosapentaenoic, 7-10-13-16-19 docosapentaenoic, docosahexaenoic (DHA), lignoceric, and nervonic acid and totals of saturated, monounsaturated, polyunsaturated, N6, and N3 fatty acids. Despite the small sample size, statistically significant correlations were observed between adipose tissue levels of alpha-carotene ($r=-0.48$, $P=.05$) and alpha-tocopherol ($r=-0.54$, $P=.02$) and pre-operative serum PSA levels. This correlation suggests that men with lower consumption of these antioxidants may have a greater tumor volume as assessed by PSA.

PILOT STUDY OF BLOOD AND TISSUE PROCESSING		
Study ID	DNA (ug)	# PBL x 10^6
NC001	202.4	8
NC023	460.8	15
NC089	652.0	20
NC067	375.6	24
NC034	210.0	3
NC078	162.0	5
NC056	463.8	8
NC155	705.4	6
NC166	377.6	34
NC045	748.0	24
NC133	522.0	10
NC111	557.6	17
NC122	464.6	11
NC177	148.8	4
NC100	471.4	40
NC144	270.4	18
LA009	146.1*	6
LA015	111.3	6
LA025	72.8	4
LA039	139.8	23
LA049	58.1	4
LA055	157.5	10
LA059	196.0	18
LA065	135.9	3

*(from 1 tube of blood)

The HIPAA regulations have been developed since our proposal was submitted and will take effect prior to initiation of case recruitment. The tumor registries in NC and LA, UNC and LSUHSC and individual hospitals and urologists' offices are interpreting these regulations and implementing systems to 1) protect patient confidentiality, 2) enable patient participation in assuring the accuracy and authorizing the sharing of their medical information and 3) requiring patient authorization for use of their research specimens for proposed or future study in a confidential and secure manner. At present, NC and LA state law allows contact of prostate cancer cases once they are submitted to the state cancer registries. However, establishing and maintaining relationships with the hospitals and urologists offices in the catchment areas of NC and LA will be critical. At present, some hospitals in LA are requiring direct contact of patients by the treating physician prior to patient contact by research study personnel. Although this appears unnecessary by law and by our interpretations of the HIPAA guidelines, we have requested an additional position to assist the enrollment specialists and research nurses by developing and maintaining relationships with hospitals (pathologists), reference laboratories, urologists and urologists' offices to assist with meeting HIPAA regulations and facilitating enrollment and participation of research subjects, release of critical clinical information (abstracted from the diagnosing urologist's office records and the diagnosing pathologist's report) and release and subsequent return of the diagnostic block(s) containing prostate biopsies.

Once accessioned, patient identifiers will be separated from all research interview data, research samples and research sample data. An honest broker system will be created to assure patient confidentiality is maintained. The clinical and research databases will be maintained on separate servers and Dr. Schell will serve as the "honest broker". The Department of Epidemiology and the UNC-Lineberger Comprehensive Cancer Center are in the process of creating this system for the Consortium within the UNC-Lineberger Comprehensive Cancer Center. Space has been identified, hardware is being purchased, positions are being created and software that exists within the School of Public Health is being customized to serve the Consortium (see above).

c. Secure 2 additional consultants to assist with evaluation of the proposal. Dr. Frank French, Professor of Pediatrics and Director, Laboratories for Reproductive Biology, will serve as an internal.

Drs. Giovannucci and Litwinn agreed to serve as external advisors. In addition, we created the following committees to assist us with the overall operation of the Consortium:

Consortium Oversight Committee			
Lutz Birnbaumer, Ph.D.[1]	NIEHS	Scientific Director	Member, National Academy of Science
William A. Darity, Ph.D.[2]	UNC	Director	The Institute of African American Research
H. Shelton Earp, M.D.[5]	UNC	Director	UNC-Lineberger Cancer Center
Ken R. Harewood, Ph.D.[3]	NCCU	Director	JLC Biomedical-Biotechnology Institute
Oliver Sartor, M.D.[4]	LSUHSC	Director	LSU-Stanley S. Scott Cancer Center
David Savitz, Ph.D.[5]	UNC	Chairman	UNC School of Public Health, Department of Epidemiology
Pelayo Correa, M.D.[4]	LSUHSC	Professor, Emeritus	Department of Pathology
Patient Advocate Committee			
Jimmy Barnes	NC	Prostate Cancer Survivor	
Robert S. Cline	NC	Prostate Cancer Survivor	
George Currie	NC	Community Activist	
John Godbolt	NC	Community Activist	
Jimmy and Linda Hinnant	NC	Prostate Cancer Survivor and Spouse	
Curtis Jackson	NC	Community Activist	
John A. Jones, Sr.	LA	Prostate Cancer Survivor	
Willie Miller	NC	Prostate Cancer Survivor	
Jim Raby	LA	Prostate Cancer Survivor	
Calvin Saulny	LA	Prostate Cancer Survivor	
Edward Washington	NC	Community Activist	
Consortium Advisory Committee			
Frank French, M.D.	UNC	Professor	androgen regulation; endocrinologist
Edward Giovannucci, M.D.	Harvard	Associate Professor	nutritional epidemiology; physician
Mark Litwin, M.D.	UCLA	Associate Professor	health outcomes research; urologist
Epidemiology Core Advisory Committee			
Vivien Chen, Ph.D.	LSUHSC	Professor	Cancer Registry Director, LA
Clarence (Ed) Davis, Ph.D.	UNC	Chairman	Biostatistics, School of Public Health
Dale Herman	UNC	Director	Cancer Registry, North Carolina

1. NIEHS Institution Support
2. African American Health Issues
3. NCCU Collaborative Opportunities

4. LSU Institutional Support
5. UNC Institutional Support

d. Reassemble the key personnel in Chapel Hill to review the proposal not later than 1 month prior to submission to insure that all members of the research team has full input.

A DOD Consortium meeting was held at UNC May 22, 2002 (the agenda is Attachment 2). By the time of this meeting, all 3 scientific Cores and 11 of 12 Projects had been submitted. We discussed and/or acted upon the following:

- specific questions regarding submission and review
- bias in Cores 2 and 3 due to specimen handling and tissue microarray creation
- pilot testing of the interview instrument
- fat aspiration
- ethical considerations regarding race-based genotyping
- the need to convene a meeting of patient advocates/ community activists (that was held June 6, 2002)
- standard (consortium-wide) definitions for CaP risk, CaP "aggressiveness", and CaP characteristics of tumor extent, tumor differentiation and tumor growth rate
- standard (consortium-wide) style, nomenclature, abbreviations and statistical analysis
- final budget
- authorship/data sharing agreement

e. Submit an excellent proposal on time that addresses the goals of the DOD Prostate Cancer Research Program and the guidelines and rules for the Prostate Cancer Consortium Award

The full proposal was submitted on June 12, 2002. Its quality was deemed sufficient for funding.

KEY RESEARCH ACCOMPLISHMENTS

- DOD Consortium proposal submitted and approved for funding
- Assembly of a team of investigators, administrative structure and scientific and lay oversight committees to facilitate the proposed studies
- Pilot study that demonstrated that AA and CA men with CaP in NC and LA would agree to participate in the proposed studies and that research specimens were of sufficient quantity and quality for the analyses proposed
- Improved method for determination of apoptosis in CaP that will allow more accurate calculation of CaP tumor growth rate
- Demonstration of adequacy for the proposed studies of sections of tissue microarray of diagnostic prostate biopsies
- Assembly of in-home interview instruments

REPORTABLE OUTCOMES

- Department of Defense Prostate Cancer Research Program, DOD-PC-012004, Racial differences in prostate cancer: Influences of health care interaction and host and tumor biology (notified November 4, 2002 of award, start date to be determined).
- Arab LA, Cohen B, Mohler JL. Prostate Cancer: Antioxidants and Tumor Characteristics. Presented at the Institute of Nutrition Annual Scientific Symposium, Chapel Hill, NC, October 28, 2002.
- Smitherman AB, Gregory CW, Mohler JL. Apoptosis levels increase after castration in the CWR22 human prostate cancer xenograft. (Submitted)

CONCLUSIONS

The Consortium Development Award allowed us to prepare a successful Consortium Award proposal and assemble the people, structure and preliminary testing/data necessary to initiate the proposed studies.

PERSONNEL RECEIVING PAY FROM THE RESEARCH EFFORT

Arab, Lenore
Chen, Vivien
Clark, Jack
Cohen, Brian
Fontham T. H. Elizabeth
Fuller, Gail
Godley, Paul
Gregory, Chris
Hu, Jennifer
Isaacs, B. William
Lantry, Jennifer
Mishel, Merle
Mohler, James
Ornstein, David
Sartor, Oliver
Schell, Michael
Schwartz, Gary
Simonsen, Neal
Smith,Gary
Su, Joseph
Talcott, James
Wargovich, J. Michael
Whang, Young
Wilson, Elizabeth
Xu, Jianfeng

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APPENDICES

1. Agenda for February 22, 2002 meeting
2. Agenda for May 22, 2002 meeting

Department of Defense Prostate Cancer Consortium
Lineberger Comprehensive Cancer Center
February 22, 2001

Overall Meeting Goals

1. Discuss the consortium, its goals and the role of each project within it
2. Determine how projects should be thematically grouped to maximize synergy and interaction
3. Develop a matrix of interactions across projects
4. Develop hypotheses for each project
5. Reach agreement on a timeline for contributions to the grant

Agenda

11:00 - 11:15 **Welcome, Overview – Jim Mohler**

<u>Host Interaction with the Healthcare System</u>

11:15 – 12:30 **Rapid Case Ascertainment**
UNC – Arab
LSU – Fontham (Simonsen), Su, Chen

12:30 – 1:00 **LUNCH**

1:00 – 1:30 **Early Detection Behavior, Health Care Access, SES, Attitudes, Beliefs, Knowledge**
UNC – Godley
JHU – Talcott

Patient-Physician Communication and Decision Making
UNC – Mishel

Alternative Medicine Use
USC – Wargovich

1:30 – 2:00 <u>Racial Differences in Diet, Androgen Axis, and Biology of the Host</u>
Diet Assessment
UNC – Arab

Serum androgens and AR Tri-nucleotide Repeats
UNC – Mohler

CaP Susceptibility Genes
NIEHS – Taylor

Mitochondrial DNA Mutations
UNC – Ornstein
NIEHS – Copeland, Tomer

Familial CaP Susceptibility Genes
JHMC – Isaacs
WFU – Xu

Markers of African-American Admixture
UNC – Smith

Proteomic Analysis of the Host
UNC – Ornstein
FDA – Chris Petricoin

DNA Repair
Hu - WFU

2:00 – 2:30 **Tumor Characteristics**

Apoptosis/Cell Proliferation/AR
UNC – Mohler

AR-Regulated Gene Expression
UNC – Gregory

AR Co-activators
UNC – Wilson

Cell Signaling Molecules
UNC – Whang

1-alpha-hydroxylase
WFU – Schwartz

Stem-like Cell Composition and HGF/cMet
UNC – Smith

2:30 – 4:00 **Other Topics of Discussion**

2:30 – 2:45 Samples Needed – Table

2:45 – 3:00 Instructions for Preparation of Proposal

3:00 – 3:15 Budget

3:15 – 3:30 Authorship and Data Sharing

3:30 – 4:00 Timeline

DOD Consortium Meeting Agenda
Lineberger Comprehensive Cancer Center
Executive Board Room
May 22, 2002
9:00 a.m. to 3:00 p.m.

9:00 – 9:15 a.m. **Welcome Overview (Mohler)**

9:15 – 10:45 a.m. **Review of Cores**

a. Administrative structure

b. Realtime communication and data sharing

c. Patient accrual strategy and monitoring

d. Pilot study results

e. Specimen storage and distribution

f. Tissue microarray pilot

Core 1: *Administration Core* (James L. Mohler)

Core 2: *Epidemiology* Core (Lenore Arab, Elizabeth Fontham)

Core 3: *Host-Tissue Procurement Core* (Gary J. Smith)

Core 4: *Tissue MicroArray and ImmunoAnaysis Core* (James L. Mohler, Bernardo Ruiz)

11:00 – 12:00 p.m. Review of Level 1: Racial Differences in Patient Healthcare Interaction (Merle Mishel)

a. Questionnaires
b. Focus groups
c. Common outcome parameters
d. Interaction between projects

Project 1: *Prostate Cancer Early Detection Behavior and Health Care Access, Socioeconomic Status, Attitudes, Beliefs, and Knowledge* (Paul Godley, James Talcott, Jack Clark)

Project 2: *Patient-Physician Communication* (Merle Mishel)

12:00 – 1:00 p.m. Lunch

1:00 – 2:00 p.m. Review of Level 2: Racial Differences in the Host (Gary J. Smith)

a. Common outcome parameters
b. Interaction between projects

Project 3: *Nutrition* (Lenore Arab, L. Joseph Su)

Project 4: *DNA Damage/Repair and Prostate Cancer Risk* (Jennifer Hu, Jack Taylor)

Project 5: *Genetic Determinants of Tumor Aggressiveness* (Jack Taylor)

Project 6: *Familial Prostate Cancer Susceptibility Genes* (William B. Isaacs, Jianfeng Xu)

Project 7: *Admixture of African and European Genetic Backgrounds* (Gary J. Smith)

Project 8: *Proteomic Analysis of the Host* (David K. Ornstein)

2:00 – 3:00 p.m. Review of Level 3: Racial Differences in Tumor Characteristics (James L. Mohler)

a. Common outcome parameters
b. Interaction between projects

Project 9: *The Androgen Axis in Prostate Cancer* (James L. Mohler)

Project 10: *Androgen Receptors Regulated Genes and Nuclear Coactivators in Prostate Cancer* (Elizabeth Wilson)

Project 11: *Expression of Cell Signaling Proteins* (Young E. Whang)

Project 12: *The Differential Role of Tissue Stem Cells in Prostate Cancer in African Americans and Caucasian Americans* (Gary J. Smith)

2:30 – 2:45 Budget

2:45 – 3:00 Authorship/Data sharing